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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/874,992	06/12/97	STAMLER J	DUK97-02M

HM12/0815
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EXAMINER	
CELSA, B	
ART UNIT	**PAPER NUMBER**
1627	18

DATE MAILED: 08/15/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

file copy

Office Action Summary

Application No.	Applicant(s)
08/874,992	Stamler et al.
Examiner	**Group Art Unit**
Bennett Celsa	1627

☒ Responsive to communication(s) filed on *May 23, 2000*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *15-17, 50, and 52-59* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *15-17, 50, and 52-59* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Amendment

Applicant's amendment dated 5/23/00 in paper no. 17 is acknowledged.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

Claims 15-17, 50 and 52-59 are currently pending and under consideration.

Outstanding Objection(s) and/or Rejection(s)

2. Claims 15-17 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over . Stamler et al, WO 93/09806 (5/93).

Stamler et al. generally teach pharmaceutical deliver of NO by administering nitrosylated protein compounds (e.g. the addition of an NO group to an SH, oxygen, carbon or nitrogen: see page 14, lines 7-12), including nitrosylated hemoglobin, which is formed by conventional means (e.g. see Stamler page 1-5) for use in relaxing smooth muscle, inhibiting platelet aggregation, promoting vasodilation and for treating/preventing cardiovascular disorders (e.g. see page 19, lines 22-25; Stamler claims 18, 20, 36, 37, 41-42, 44, 45; etc.). Cardiovascular disorders include those within the scope of the presently claimed invention (e.g. myocardial infarction, pulmonary embolism, myocardial infarction etc. E.g. See page 18, lines 5-11).

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to utilize nitrosylated hemoglobin for purposes of inhibiting

platelet activation, preventing thrombus formation or for treating platelet activation or adherence disorders including cardiovascular disorders (e.g. infarction, embolism etc.) by administration of ntirosylated hemoglobin to a patient in need thereof as described in the Stamler reference.

3. Claims 15-16 are rejected under 35 U.S.C. 103(a) as obvious over Stamler et al, WO 93/09806 (5/93) and Kaesenmeyer, U.S.Pat. No. 5,543,430 (8/96: filed 10/94). .

Stamler et al. generally teach pharmaceutical delivery of NO by administering nitrosylated protein compounds (e.g. the addition of an NO group to an SH, oxygen, carbon or nitrogen: see page 14, lines 7-12), including nitrosylated hemoglobin formed by conventional means (e.g. see Stamler page 1-5), for use in relaxing smooth muscle, inhibiting platelet aggregation (e.g. preventing thrombus formation), promoting vasodilation and for treating/preventing cardiovascular disorders (e.g. see page 19, lines 22-25; Stamler claims 18, 20, 36, 37, 41-42, 44, 45; etc.). Cardiovascular disorders include those within the scope of the presently claimed invention (e.g. myocardial infarction, pulmonary embolism, myocardial infarction etc. E.g. See page 18, lines 5-11).

The Stamler reference differs from the presently claimed invention which additionally encompasses the use of nitrated hemoglobin as the NO donor to effect the same function (e.g. relaxing smooth muscle, inhibiting platelet aggregation, preventing thrombus formation, promoting vasodilation and for treating/preventing cardiovascular disorders).

However, the Stamler reference, besides generically describing the use of nitrosylated proteins (e.g. nitrosylhemoglbins), additionally suggests the use of S-nitrosylhemoblin, for relaxing smooth muscle, inhibiting platelet aggregation, promoting vasodilation and for treating/preventing cardiovascular disorders

The Stamler et al. generic teaching of using NO donor nitrosylated protein compounds, including nitrosylated hemoglobins and methemoglobins, and a species of specifically nitrosylated hemoglobin (e.g. S-nitrosylated) would motivate one of ordinary skill in the art to utilize other nitrosylated hemoglobins which would be deemed to be functionally equivalent as NO donating compounds.

Thus, the selection of a species of NO donating hemoglobin is a matter of choice to one of ordinary skill in the art since the Stamler reference teaches the functionally equivalent use of nitrosylated proteins, including hemoglobins, as well as individually nitrosylated hemoglobin species including thionitrosylated hemoglobin.

In this regard, the use of oxidized forms of NO (e.g. nitrites/nitrates) as functionally equivalent NO donors is conventionally known in the art (E.g. See Kaesenmeyer at col. 6).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to substitute nitrated hemoglobins for nitrosohemoglobins in the methods as disclosed by Stamler with a reasonable expectation of success due to functional equivalency of nitrites/nitrates as NO donating compounds.

4. Claims 15-17 and 53-59 are rejected under 35 U.S.C. 103(a) as obvious over Stamler et al, WO 93/09806 (5/93) alone and if necessary further in view of the specification admission as to prior art on pages 37-39, Kaesenmeyer, U.S.Pat. No. 5,543,430 (8/96: filed 10/94), Moore et al., J.Biol. Chem. Vol. 251, No. 9, (5/76) pages 2788-2794, Sharma et al., J. Biol. Chem. Vol. 253, No. 18 (9/78) pages 6467-72 and Wade et al. Chem. Res Tox. 1990 Vol. 3, pages 289-291.

Stamler et al. generally teach pharmaceutical delivery of NO by administering nitrosylated protein compounds (e.g. the addition of an NO group to an SH, oxygen, carbon or nitrogen: see page 14, lines 7-12), including nitrosylated hemoglobin formed by conventional means (e.g. see Stamler page 1-5), for use in relaxing smooth muscle, inhibiting platelet aggregation (e.g. preventing thrombus formation), promoting vasodilation and for treating/preventing cardiovascular disorders (e.g. see page 19, lines 22-25; Stamler claims 18, 20, 36, 37, 41-42, 44, 45; etc.). Cardiovascular disorders include those within the scope of the presently claimed invention (e.g. myocardial infarction, pulmonary embolism, myocardial infarction etc. E.g. See page 18, lines 5-11).

Additionally, the Stamler reference, besides generically describing the use of nitrosylated proteins (e.g. nitrosylhemoglbins), additionally suggests the use of S-nitrosylhemoblin, for relaxing smooth muscle, inhibiting platelet aggregation, promoting vasodilation and for treating/preventing cardiovascular disorders, the Stamler reference fails to disclose other specific species nitrosylated hemoglobins (e.g. nitrosylhemoglobin, polynitrosated hemoglobin, and nitrosated methemoglobin).

Further, Stamler discloses different methods for thiol nitrosylation of proteins (as disclosed on page 30-31) which include:

1. reaction of nitrosylating agent (e.g. equimolar amounts of acidic NaNo2 as nitrosating agent in a buffered saline at pH 7.4 for tPA);

2. exposure of the protein (e.g. tPA to NO gas in buffered saline)

as well as Example 19 with respect to hemoglobin (e.g. See Example 19 on pages 58-59), which utilizes selection of a low molecular weight S-nitrosothiol (e.g. SNOAC) as nitrosating agent.

Optimization, e.g. using "excess nitrosating agent" or higher pH values (e.g. pH 7.4) than that utilized in the specific thionitrosylated hemoglobin example (e.g. pH 6.9 Example 19) is within the skill of the art and is further suggested by Stamler since thionitrosylated proteins are known to be stable under physiological conditions (e.g. TBS, pH 7.4, room temperature: see page 31). See also other Examples which utilize physiological conditions in analogous steps .E.g. page 30, lines 20-27; page 33, lines 20-26).

Additionally, the specification summary of the prior art on pages 37-39 disclose art-recognized techniques for formulating various oxidized and deoxidized nitrosylated hemoglobins in which hemoglobin is nitrosylated on different portions of the compound.

Similarly, Castro et al. Chem. Res Tox. 1990 Vol. 3, pages 289-291 reference discloses a method of transferring the nitrosyl group to sulfur (as well as oxygen, nitrogen and sulfur) of heme proteins, including hemoglobin to thus form, polynitrosated hemoglobins, including SNO-hemoglobins.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to utilize oxidized/deoxided S-nitrosylated hemoglobin for relaxing smooth muscle, inhibiting platelet aggregation, promoting vasodilation and for treating/preventing cardiovascular disorders as suggested by the Stamler reference.

Although, the Stamler reference, generically describes the use of nitrosylated proteins (e.g. nitrosylhemoglbins), and suggests the use of S-nitrosylhemoblin, for relaxing smooth muscle, inhibiting platelet aggregation, promoting vasodilation and for treating/preventing cardiovascular disorders, the Stamler reference fails to disclose other individual species of nitrosylated hemoglobins (e.g. nitrosylhemoglobin, polynitrosated hemoglobin, and nitrosated methemoglobin).

However, the formation of nitrosated hemoglobins, including, oxidized/deoxided nitrosylhemoglobin, polynitrosated hemoglobin, and nitrosated methemoglobin is within the skill of the art. E.g. See Stamler reference on pages 1-5 ; specification admission on pages 37-39; and Moore et al. and Sharma et al. disclosing "stock nitrosylhemoglobin" which comprises nitrosyl-deoxyhemoglobin.

Further, the Stamler et al. generic teaching of using NO donor nitrosylated protein compounds, including nitrosylated hemoglobins and methemoglobins, and a species of specifically nitrosylated hemoglobin (e.g. S-nitrosylated) would motivate one of ordinary skill in the art to utilize other nitrosylated hemoglobins which would be deemed to be functionally equivalent as NO donating compounds for use in relaxing smooth muscle and inhibiting platelet aggregation.

Thus, the selection of a species of NO donating hemoglobin is a matter of choice to one of ordinary skill in the arts since the Stamler reference teaches the functionally equivalent use of nitrosylated hemoglobins including thionitrosylated hemoglobin.

Further, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to utilize oxidized/deoxided S-nitrosylated hemoglobin as well as other nitrosylated hemoglobin species (e.g. polynitrosated hemoglobin, nitrosylhemoglobin) for relaxing smooth muscle, inhibiting platelet aggregation, promoting vasodilation and for treating/preventing cardiovascular disorders since these other nitrosylated hemoglobin species would be expected to act equivalently as NO donating compounds.

Discussion

Applicant's arguments directed to the above obviousness rejections were considered but deemed nonpersuasive for the following reasons.

Applicant argues that the Declaration evidence (e.g. by Dr. Stamler) is sufficient to overcome the above rejections of record.

Regarding the Stamler document as interpreted by the Examiner in view of the Stamler Declaration evidence it appears to the Examiner that the Stamler example when taken separately and in view of the entire document teaching of S-nitrosylation of different proteins, including hemoglobin would suggest reacting SNOAc (e.g. S-nitroso-N acetylcysteine) with hemoglobin in equimolar amounts at pH 6.9. Upon careful reevaluation of the Stamler Declaration evidence and especially the reproduction of the above reference experimental conditions and the inability

to produce S-nitrosylation *without detectable heme Fe oxidation*, the Examiner believes that the above reference conditions which lack the "critical" requisite pH range (e.g. 7.4-9.2) as disclosed is nonenabled for producing compositions consisting essentially of S-nitrosylated hemoglobin *without detectable heme Fe oxidation.*

However, Applicant's arguments are clearly not commensurate in scope to the presently claimed invention which is not specifically limited to the use of compositions which "consist essentially of" S-nitrosylated hemoglobin w/o detectable oxidation of the heme to which the Declarant evidence establishes the nonenablement of the Stamler reference to produce.

Additionally, the method of use claims are not so limited to the use of " S-nitrosylated hemoglobin w/o detectable oxidation of the heme.

Applicant's declaration evidence directed to the nonenablement of the Stamler WO 93/09806 to produce S-nitrosylated hemoglobin is simply not commensurate in scope to the presently claimed invention (e.g. claims other than 50 and 52) since the use of compositions comprising "nitrosated or nitrated hemoglobin" clearly encompass many species in addition to that of S-nitrosylated hemoglobin species.

Applicant's argument that prior to the present invention, the NO donor activity of nitrosated hemoglobins was not known is specifically rebutted by the WO 93/09806 reference which teaches the reaction of low molecular weight thiols with various proteins, including hemoglobin, to form NO-donating compounds (e.g. see WO 93/09806 abstract and page 1).

Applicant's argument regarding the Moore et al. And Sharma et al. reference taken alone (e.g. as not teaching NO donation of nitrosylated/nitrosated hemoglobins) is not persuasive since the teaching of these reference are combined with the WO 93.09806 reference which suggests the ability of nitrosylated/nitrosated proteins (e.g. hemoglobin) to act as NO donors.

Similarly, applicant's arguments directed to the Stamler reference (WO 93/09806) taken alone (e.g. claims 10-15) was considered but deemed nonpersuasive.

Applicant argues that the Stamler reference methods as disclosed on pages 30-31 would fail to produce S-nitrosylated hemoglobin.

However, the scope of applicant's claims are NOT limited to S-nitrosylated hemoglobin (w/o detectable heme oxidation) but are generically drawn to nitrosylated/nitrated hemoglobin to which the Stamler reference teaches can be used in an NO donating capacity (e.g. See Stamler reference pages 1-4).

To the extent that applicant is arguing that only S-nitroslated hemoglobins can be used as NO donors; such an argument is inconsistent with the presently claimed invention which is not so limited nor is such an argument consistent with the Stamler WO 93 reference which suggests otherwise.

Applicant argues that the WO 93/09806 fails to teach a "successful syntheses of S-nitrosylated, O-nitrosylated, C-nitrosylated or N-nitrosylated hemoglobin is taught".

However, applicant's declaration evidence directed to demonstrate nonenablement is strictly directed to a single embodiment of the Stamler reference; e.g. a single example directed to making S-nitrosylated hemoglobin.

There is no evidence of record to dispute the other Stamler reference methods provided therein regarding the syntheses of other nitrosated/nitrated hemoglobins within the scope of the presently claimed invention. In this regard, applicant is directed to the Moore et al., Sharma et and Wade et al. References which disclose methods for synthesizing nitrosated/nitrated hemoglobin species which are capable of acting as NO-donating compounds.

Turning to the Kaesenmeyer reference patent, applicant argues that this reference is deficient since it fails to mention any form of hemoglobin or any nitrosoprotein.

In response to applicant's arguments against the Kaesenmeyer reference individually, one cannot show nonobviousness by attacking a reference individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant's argument as to what the state of the prior art was (e.g. Kaplan et al. And Greenber References) regarding nitrosated/nitrated hemoglobin scavenger activity is not relevant to the above obviousness rejections which is directed to the ability of nitrated/nitrosated proteins, including hemoglobin, to act as an NO-donating compound as taught by the Stamler WO 93 reference.

Applicant argues that the WO 93/09806 reference is limited to teaching only one species of hemoglobin e.g. S-nitrosohemoglobin.

However, by focusing only on one embodiment, applicant is impermissibly failing to consider the WO 93/09806 reference teaching taken as a whole.

As described in the above obviousness rejections, the Stamler reference generally teaches the pharmaceutical delivery of NO by administering nitrosylated protein compounds (e.g. the addition of an NO group to an SH, oxygen, carbon or nitrogen: see page 14, lines 7-12), including nitrosylated hemoglobin formed by conventional means (e.g. see Stamler page 1-5), for use in relaxing smooth muscle, inhibiting platelet aggregation (e.g. preventing thrombus formation), promoting vasodilation and for treating/preventing cardiovascular disorders (e.g. see page 19, lines 22-25; Stamler claims 18, 20, 36, 37, 41-42, 44, 45; etc.)

The Stamler reference also discloses various "conventional means" of making nitrosylated hemoglobin to arrive at nitrosated hemoglobins within the scope of the presently claimed invention.

Applicant argues that the recitation of "if necessary" in the preamble of the rejection requires clarification.

The term "if necessary" is being used in the same nature as the term "alternatively" which is believed to be consistent with the content of the obviousness rejections recited above.

Applicant is confused as far as what is meant by "the specification admission as to prior art on pages 37-39" arguing that the specification fails to teach the making of nitosated or nitrated hemoglobins or the use thereof.

The Examiner regrets any confusion resulting from the use of the specification admission. As discussed in the obviousness rejection above, the specification summary of the prior art on pages 37-39 disclose art-recognized techniques for formulating various oxidized and deoxidized nitrosylated hemoglobins in which hemoglobin is nitrosylated on different portions of the compound. In this regard, the Examiner was simply referring to the specification citation on page 37 of the Simon and Stamler references which illustrate conventionally available techniques for nitrosating proteins which would be applicable to hemoglobin (e.g. as a protein) for use in methods suggested by the WO 93/09806 reference.

Applicant proceeds to argue that the Moore et al. And , Sharma et al. References fail to suggest physiological effect or any other NO donating capability.

However, it is clear from the above obviousness rejection that the Stamler reference teaching of the NO-donating ability of nitrosylated proteins, including hemoglobin, is being combined with the Moore and Sharma reference methods of producing nitrosylated hemoglobins within the scope of the presently claimed invention.

As pointed out in the obviousness rejection above, the Castro et al. Chem. Res Tox. 1990 Vol. 3, pages 289-291 reference discloses a method of transferring the nitrosyl group to sulfur (as

well as oxygen, nitrogen and sulfur) of heme proteins, including hemoglobin to thus form, polynitrosated hemoglobins, including SNO-hemoglobins.

With respect to the Castro reference applicant argues that this reference fails to describe a stable product of a reaction between a species of nitric oxide with a site on Hb other than the heme Fe.

As recited above, the Castro reference provides a means to make " (poly)nitrosated" hemoglobins within the scope of the presently claimed invention. Additionally, applicant's argument is not commensurate in scope to the presently claimed invention which is not limited to S-nitrosylated hemoglobins or nitrosylated hemoglobins which do not contain nitrosylated heme Fe. Further, no showing has been made (e.g. nonenablement) calling into question the ability of the Castro method to nitrosylate to S, O, and N atoms as taught by the reference .

With regard, to the Stamler reference, applicant argues that although Stamler discloses different methods for thiol nitrosylation (e.g. as discussed on page 30-31); none of these methods would produce SNO-hemoglobin.

Initially, it is again pointed out that applicant's claims are broader than applicant's argument since they encompass nitrosylated hemoglobin species other than SNO-hemoglobin. Additionally, even in the most preferred claimed embodiments (e.g. claims 50-51), such claims are broadly directed to compositions that "comprise" SNO-hemoglobin; which would include mixtures of different nitrosylated hemoglobin compounds as long as somewhere within this

mixture there exists SNO-hemoglobin. Further, there is no claim limitation requiring that the Fe not be nitrosylated.

Accordingly, the Stamler reference methods as well as the other reference methods of record (e.g. the secondary reference methods and those reference methods by specification admission) must produce nitrosylated hemoglobin compositions within the scope of the presently claimed invention.

Applicant then argues that "the literature offer methods to produce proteins with NO bound to the heme Fe, to produce nitrosyl heme proteins such as nitrosylhemoglobin".

Even, *assuming arguendo*, applicant is correct, applicant's claims still encompass "proteins with NO bound to the heme", such as nitrosylhemoglobin (e.g. see present claims 53 and 56), as well as NO bound to other portions of hemoglobin molecule, due to the presence of reactive moieties.

Accordingly, the above obviousness rejections are hereby retained.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat (art unit 1627), can be reached at (703)308-0570.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1627)

August 11, 2000

BENNETT CELSA
PRIMARY EXAMINER